systemic lupus erythematosus, multiple sclerosis, autoimmune hemolytic anemia and autoimmune thyroiditis.

Cancel claims 3-8 without prejudice or disclaimer.

9. (Amended) The method of claim [7] 1, wherein said treatment suppresses the symptoms of said autoimmune diseases in said [animal] human.

Cancel claim 10 without prejudice or disclaimer.

11. (Unchanged) The method of claim 1 wherein said autoantigen is administered orally.

12. (Unchanged) The method of claim 1 wherein said autoantigen is administered enterally.

13. (Unchanged) The method of claim 1 wherein said autoimmune disease is multiple sclerosis.

Cancel claim 14 without prejudice or disclaimer.

15. (Amended) The method of claim 13 wherein said autoantigen is myelin basic protein (MBP), a biologically active fragment of MBP [, or an analog of MBP].

16. (Amended) The method of claim 15 wherein said biologically active fragment of MBP is a non-encephalitogenic fragment of MBP.

17. (Amended) The method of claim 16 wherein said non-encephalitogenic fragment of MBP comprises amino acids 1-37 of MBP, or [a biologically active] an orally immunosuppressive portion thereof.

18. (Unchanged) The method of claim 17 wherein biologically active portion of MBP comprises the region between

diseases recited in the claims and do not support is effectiveness for humans. Furthermore, according to the Examiner, a number of factors would cause a person of ordinary skill in the art not to expect that the claimed method would be valid (i.e., operative):

(1) genetic diversity of humans and animals;

(2) absence of suitable animal models for many autoimmune diseases and absence of human data;

(3) failure of the prior art to devise effective treatments for these diseases;

(4) absence of evidence that tolerization would prevent such diseases;

(5) absence of evidence showing that a treatment effective for one autoimmune disease would be effective for another;

(6) absence of a teaching in the specification of specific autoantigens that are associated with each particular autoimmune disease.

(7) absence of tests demonstrating whether a particular autoantigen would induce the appropriate immunoprotective response against a particular autoimmune disease and would not cause adverse side-effects in the host.

This rejection is respectfully traversed, and the Examiner's concerns are addressed below:

(1) Genetic Diversity of Humans and Animals

The fact that humans and animals become tolerized to antigens found in food by the process of ingesting and digesting

the food has been known since 1911. The present invention has discovered that oral tolerization to autoantigens is effected by a mechanism that is common to rodent and human immune systems. In addition, there have been sufficient tests, including clinical tests, involving a number of autoimmune conditions to demonstrate that the claimed oral tolerization method is truly effective and is not an artifact caused by the genetic identity of the mammal group tested. Indeed, the present method is independent in its effectiveness from genetic identity or diversity.

All of this is discussed in more detail below and is declared to by Dr. Howard L. Weiner, a co-inventor of the present application.

(2) Animal Models and In Vitro Assays

A number of rodent models for autoimmune disease already exists. These include induced models, such as EAE for multiple sclerosis, EAU for uveoretihitis, collagen-induced arthritis and adjuvant arthritis for rheumatoid arthritis, and DD mouse model for the autoimmune phase of Type 1 diabetes; and spontaneous models, such as the NOD mouse model for Type 1 diabetes.

Of course, no animal model is ever perfect nor is it scientifically or medically sound to consider a human disease to be identical to a model for it. However, the work of the present inventors has now served to validate rodent models as a good testing ground for oral tolerization treatments for cell-mediated autoimmune diseases. This was done by steps towards elucidating the mechanism of oral tolerization with particular reference to

autoimmune diseases.

The present inventors have discovered that T-suppressor cells are elicited after ingestion of the autoantigen, i.e. that oral tolerization involves active suppression (as opposed to passive suppression a/k/a T-cell anergy). This discovery was first based on the finding that oral tolerization could be adoptively transferred, which would imply that T-suppressors are involved.

The present inventors have also established that the suppressor T-cells, which are specific to the orally administered antigen are targeted to the locus of immune attack where they release the immune suppressive factor TGF-b, which in turn shuts down immune responses in that locality in a nonspecific manner. All of these events are common to rodent and human immune systems and therefore serve to validate the rodent models as predictors of oral tolerizing agents and methods.

More important, the present inventors have discovered that oral administration of an autoantigen (or of the disease-inducing determinant of an autoantigen) is not necessary. All that is necessary is that an antigen specific for the afflicted tissue (and capable of eliciting T-suppressor cells i.e. possessing suppressive epitopes) be administered. They termed this phenomenon "bystander suppression"(see copending application Ser. No. 843,752 filed 2/28/92). Bystander suppression further validates the rodent model because it shows that oral tolerization is independent of the particular antigen used to orally tolerize (as long as it is tissue-specific and possesses suppressive determinants) and

therefore the results observed in rodents are generally applicable regardless of e.g. amino acid sequence differences between human and rodent proteins.

(3) Failure of the Prior Art - Human Data

The Examiner contends that the failure of the prior art to devise effective treatments for autoimmune disease makes the present invention unbelievable to the extent that it is based only on animal data.

Applicants respectfully disagree. The failure of the prior art constitutes evidence of unobviousness for the present invention not evidence of incredibility.

Moreover, the present inventors now have limited human area (from 30 patents, three different autoimmune diseases, three different investigators in three different institutions) which show effectiveness of oral tolerization in humans. The best results have been observed with uveoretinitis patients but very encouraging results have also been observed with multiple sclerosis patients and the prospects look very favorable for uveoretinitis patients (only two uveoretinitis patients have been orally treated so far). In addition, two very large Type 1 diabetes clinical studies are being planned, where oral tolerization (using insulin) will be used to halt autoimmune destruction of pancreatic beta cells in patients who are not yet dependent on extraneous insulin (i.e. who still have at least some pancreatic beta cell function). These studies (which involve children as well as adults) would not have been approved by the Institutional Review Boards of the sponsoring

institutions unless there was the expectation that oral tolerization would be effective.

(4) Absence of Evidence of Prevention

Prevention was removed from the present claims.

(5) Absence of Evidence that Oral Tolerization is Effective for Other Autoimmune Diseases

Such evidence exists in the generality of the mechanism of suppresion, in the fact that use of an autoantigen is not necessary and in the fact that oral tolerization has been clinically tested in humans for three different autoimmune conditions. See items (2) and (3) above.

In addition, oral tolerization for the autoimmune phase of Type 1 diabetes has been successfully tried in the autoimmune model by the present inventors and their coworkers (see copending patent application Ser. No. 595,468 filed 10/10/90).

(6) Absence of Identification of Specific Autoantigens

The present specification discloses a limited number of autoantigens but a broad inventive concept. The broad concept, as recited in claim 1 is independent of the particular autoimmune disease and the particular autoantigen involved. Therefore, the broad claims are adequately supported. Furthermore, due to bystander suppression, a person of ordinary skill would not have any difficulty in finding antigens that are effective oral tolerizers. Thus if a person of ordinary skill in the art read the present specifications and decided to try to find the autoantigen for Type 1 diabetes, all that person would have to do would be to feed a few NOD mice pancreatic beta cells or cell extracts or

isolated tissue-specific antigens expressed in such cells and an effective antigen could easily be found (despite the fact that its technical characterization as an autoantigen could be erroneous).

(7) Absence of Tests Showing Presence of Immunoprotective Response and Absence of Side-Effects

The Examiner will appreciate that the possibility of side-effects from feeding a person a small amount of a protein is extremely low.

Tests showing effectiveness *in vitro* and *in vivo* have been described in items (2), (3), (5) and (6) above.

The 35 U.S.C. §112, First Paragraph Rejection

The claims have been rejected under 35 U.S.C. §112, first paragraph. The Examiner is of the opinion that the claims are not enabled other than for whole MBP and the MBP fragment (1-37). This rejection is respectfully traversed.

References to MBP "analogs" have been deleted from the claims.

The amino acid sequence of MBP has long been known for several mammalian species including mouse, rat, rabbit, human, chick and guinea-pig. It has long been well-known to construct overlapping peptides corresponding to fragments of the MBP amino-acid sequence using e.g. solid phase peptide synthesis. Such peptides can be tested for immunosuppressive properties by no more than routine experimentation involving the rodent assay described in the specification. It is submitted that a person of ordinary

skill would be able to make and use the invention with no more than routine experimentation.

The 35 U.S.C. §112, Second Paragraph Rejection

Claim 1 has been amended to remove analogs. "Fragments" is not indefinite any more than "autoantigen" is indefinite. It is true that both terms are broad. But breath is not tantamount to indefiniteness.

In addition, the term "autoantigen" has been defined in the specification, p. 6.

Claims 1, 15-16 and 19 have been amended to remove "biologically active fragments."

Claim 2 which recites a list of autoimmune diseases is not indefinite, it is only broad. Claim 2 is a generic claim containing a perfectly legitimate Markush group.

The Art Rejections

Claims 1-2 and 6-18 have been rejected under 35 U.S.C. §103 as unpatentable over the combination of Campbell in view of Whitacre and, optionally, further in view of Nagler-Anderson. This rejection is respectfully traversed.

Campbell discloses intravenous administration of MBP to human patients. This is no way suggests oral administration to humans. Tolerance is dependent on mode of administration. The mechanism of intravenous tolerance is totally different from that of oral tolerance: intraveous tolerance is elicited via T-cell

energy i.e. induction of a state of immune unresponsivensss among T-cells; oral tolerance on the other hand is elicited via induction of antigen-specific T-suppressor cells. Furthermore, there is now evidence that the parts of autoantigens that induce oral tolerance are different from those that induce intravenous tolerance. Therefore, the fact that Campbell used MBP intraveneously contains no teaching whatsoever about any other method of antigen administration.

Whitacre discloses oral administration of MBP to rats to suppress subsequent induction of EAE, i.e., preventively not therapeutically. Whitacre also states that the thus induced oral tolerance could not be adoptively transferred (could not be transferred following *in vitro* culture with MBP) and attributes the oral tolerance to a state of "antigen-specific unresponsiveness," i.e. T-cell anergy not T-suppressor cell elicitation.

Whitacre was incorrect about the adoptive transferability of oral tolerance. She has finally admitted this but not before she published papers (1987 and 1991) attributing her results to clonal anergy (i.e. T-cell anergy). As we explained above, the results on the rat model have applicability to humans because events and pathways common to humans and rodents are operating in induction of oral tolerance. But Whitacre's teaching of "unresponsiveness" negates this and removes the expectiation that the oral treatment would be effective for human disease.

Other investigators, including Nagler-Anderson (p. 7445, Right col. and reference 16) have reported failure to suppress the

animal model disease after induction. Therefore, it would not have been obvious to extrapolate Whitacre's teachings to humans.

The disclosure of Nagler-Anderson parallels that of Whitacre except a different disease model (collagen-induced arthritis, a model for human rheumatod arthritis) and a different oral tolerizaer (collagen) are involved. Nagler-Anderson was also unable to adoptively transfer the orally induced tolerance and tentatively attempted to attribute the tolerance to down regulation of the humoral response, despite the fact that others had suggested that orally-induced tolerance to alloantigens (not autoantigens) might be T-suppressor cell mediated.

In view of this, it would not have been obvious to conmbine the teachings oif Campbell and Whitacre (and/or Nagler-anderson) to yield the subject of the present claims. These references are not combinable and even if combined yield at most an invitation to experiment with no reasonable expectation of success.

A favorable determination is respectfully solicited.

Respectfully submitted,

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